Outline

Lipid hypothesis for atherogenesis

Studies in experimental animals:
Early findings that led to these studies

- cholesterol is the substance that accumulates in atherosclerotic lesions
- blood cholesterol was elevated in individuals with premature atherosclerosis,
- cholesterol and saturated fat in the diet together promote atherosclerotic lesion development

Animal models for studies of atherosclerosis:

- Rabbits are hypersensitive to dietary cholesterol and rapidly develop arterial lesions
- Rats and mice are naturally resistant to diet-induced atherosclerosis
- Pigs are large animal models and while some strains are resistant, others are susceptible to diet-induced atherosclerosis with many phenotypic similarities to nonhuman primates
- Several species of nonhuman primates are sensitive to diet-induced atherosclerosis and have many phylogenetic similarities to man
- Genetically engineered mouse models of atherosclerosis are appealing due to the ability to examine molecular mechanisms of diet-induced atherosclerosis in these animals

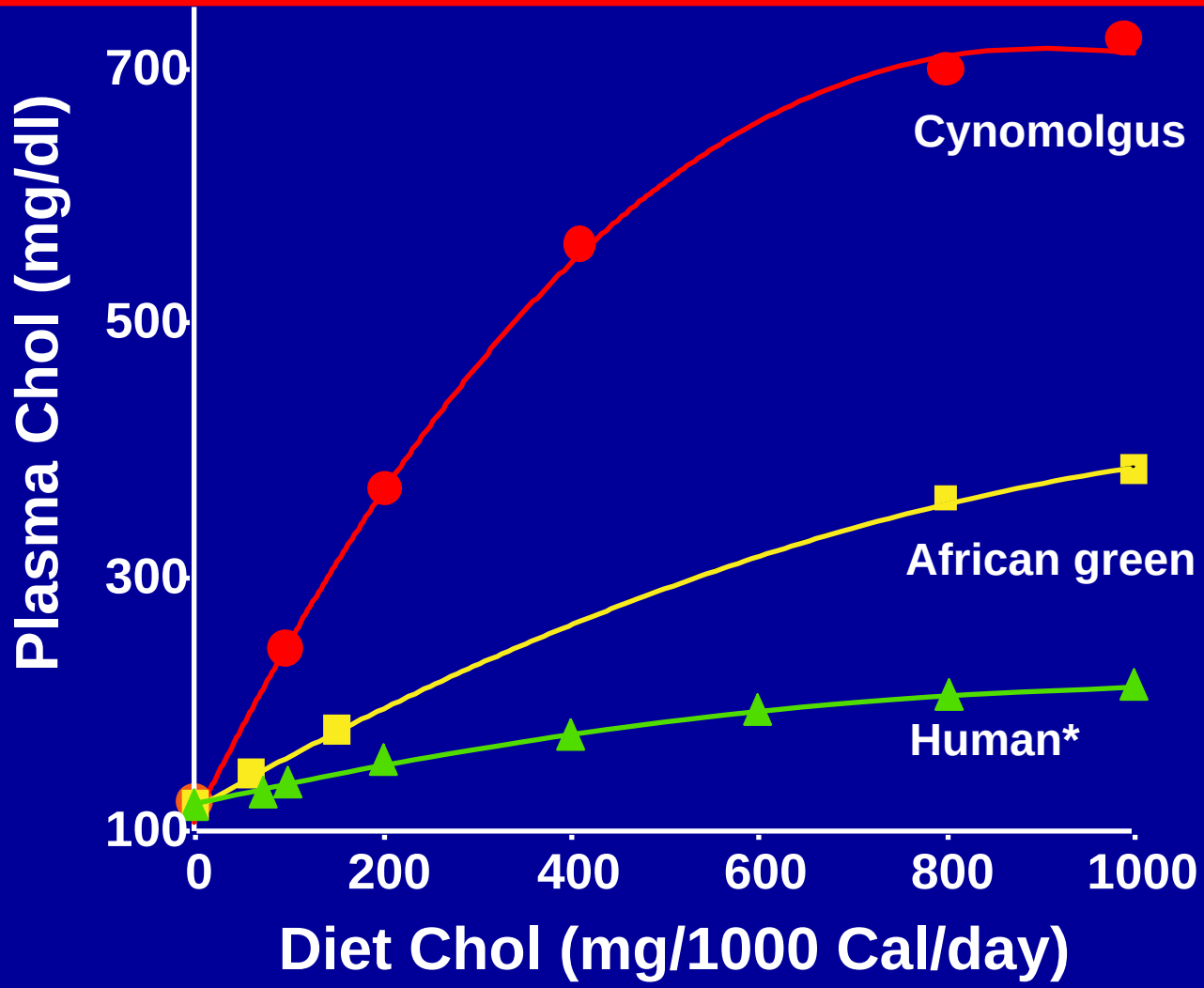
Diet-induced atherosclerosis in monkeys

- Cholesterol in diet is required
- Demonstrated specificity to type of fat
- Hepatic ACAT2 and CE secretion mediates diet-induced atherogenicity

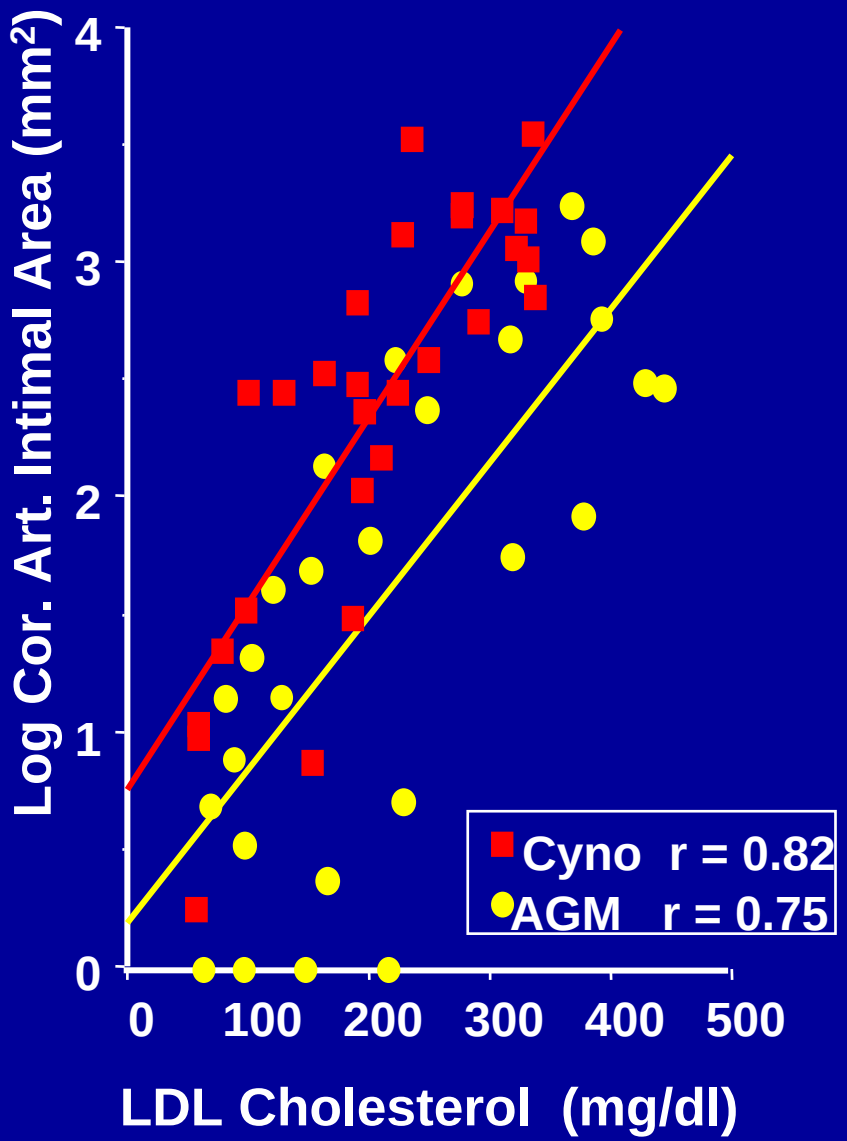
Atherosclerosis in Mice

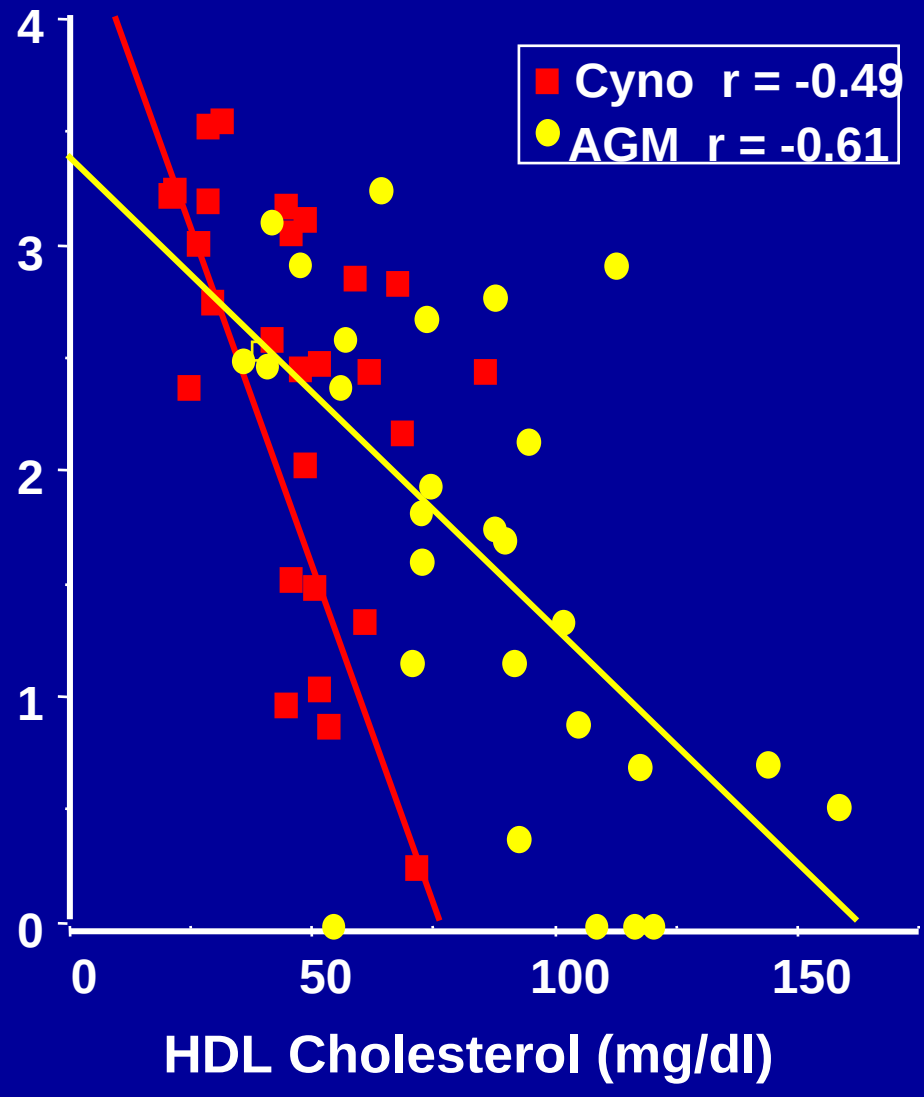
- Dietary fat and cholesterol similarities to monkeys
- Gene deletion of ACAT2 reduces atherosclerosis and eliminates hepatic CE secretion

Dietary cholesterol sensitivity is species dependent in primates

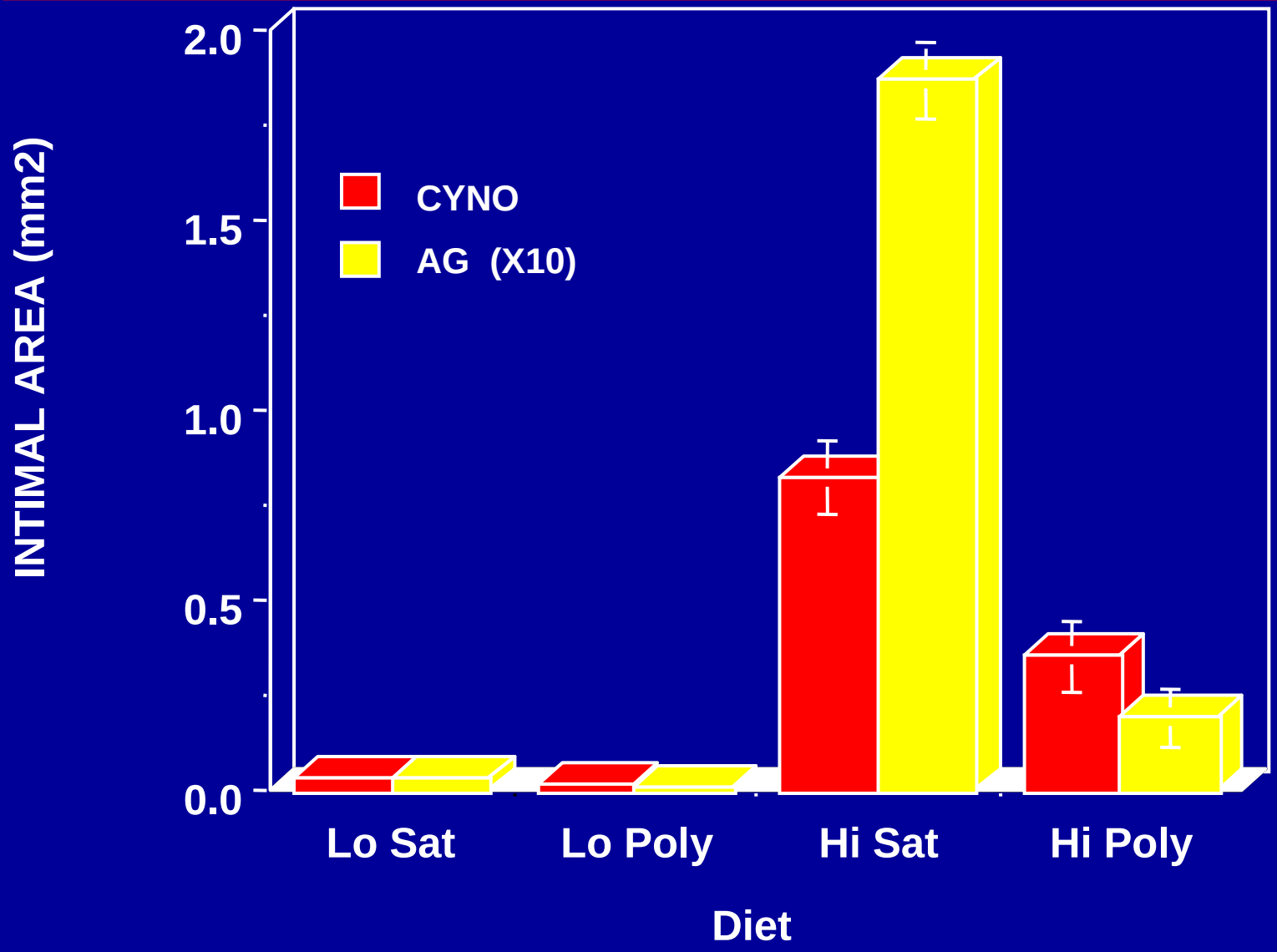


LDL Promote and HDL Protect Against Coronary Artery Atherosclerosis in Primates

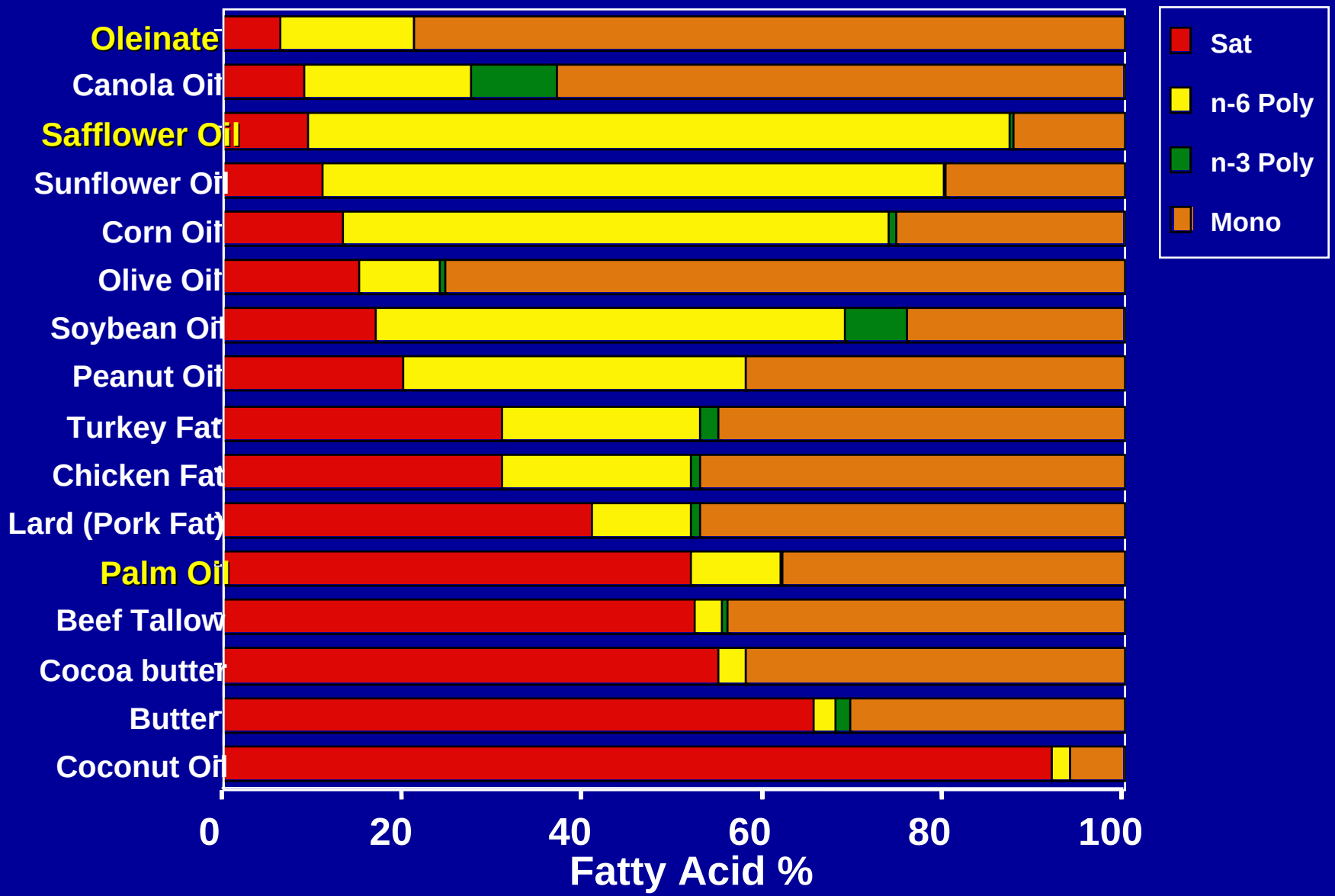




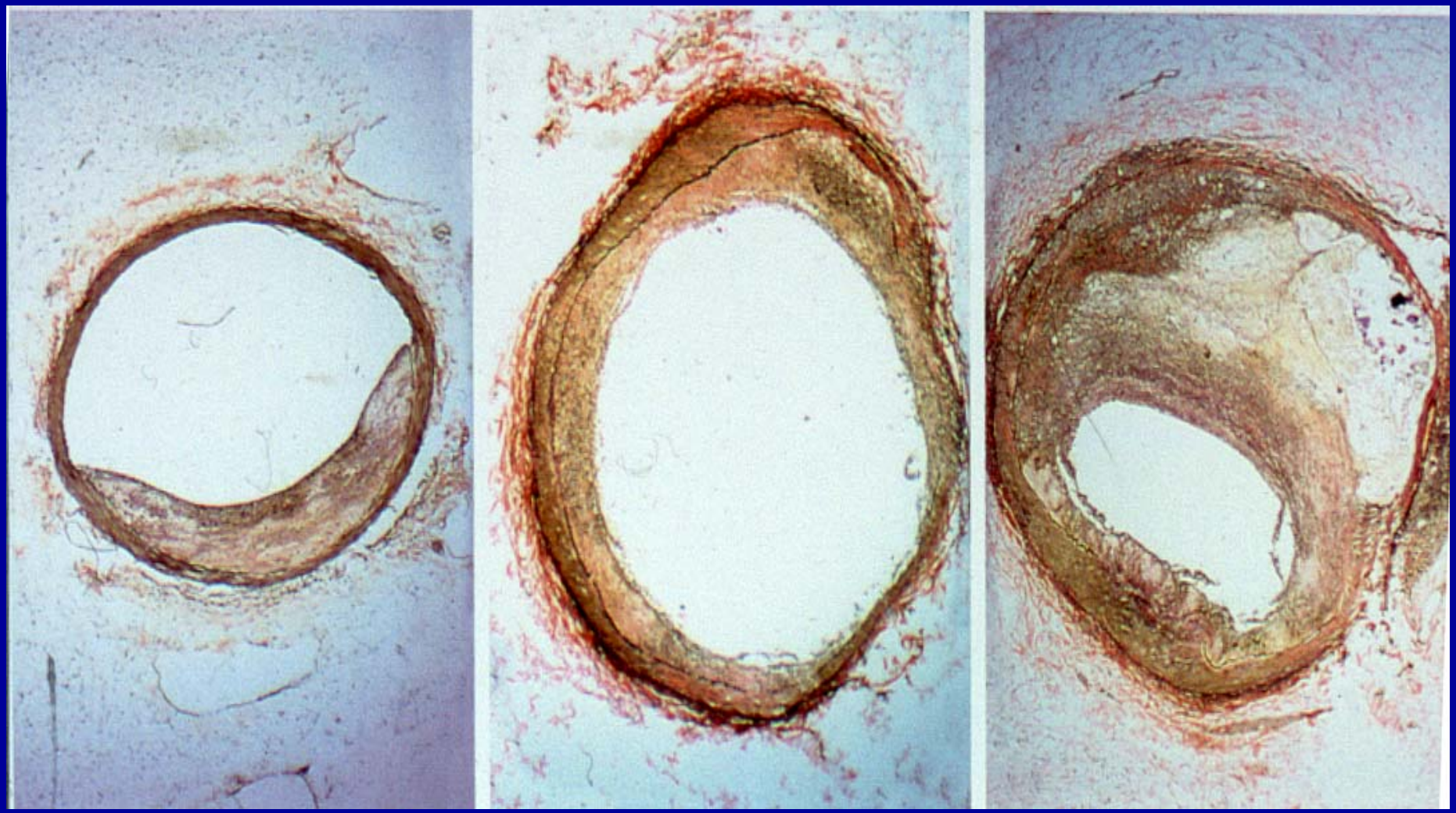
Coronary Artery Atherosclerosis Develops in Monkeys Only When Diets Contain Cholesterol; Dietary Polyunsaturated vs. Saturated Fat Protects



Fatty Acid Composition of Fats and Oils

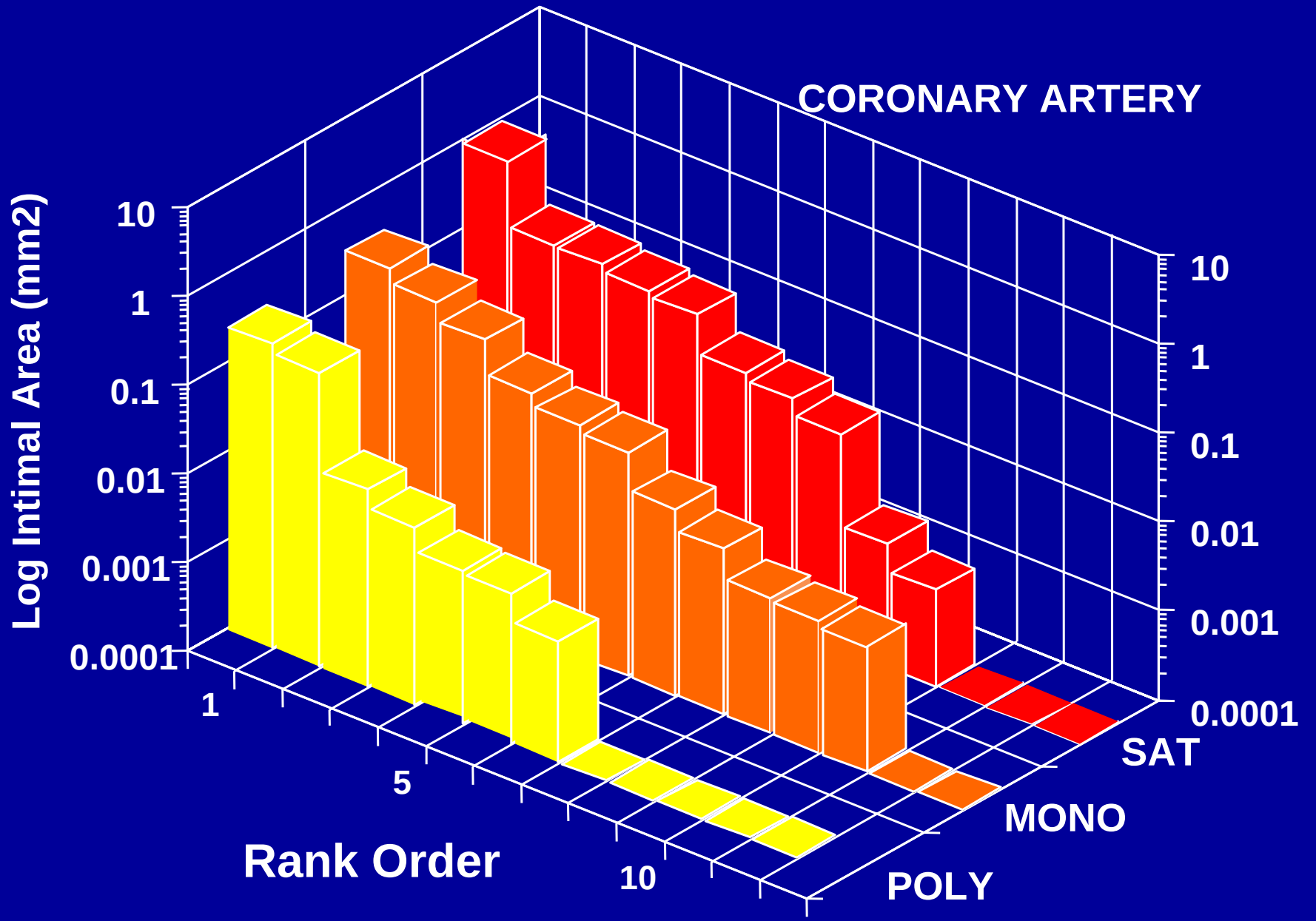


Coronary Artery Atherosclerosis is More Advanced in Animals Fed Dietary Saturated and Monounsaturated Fat

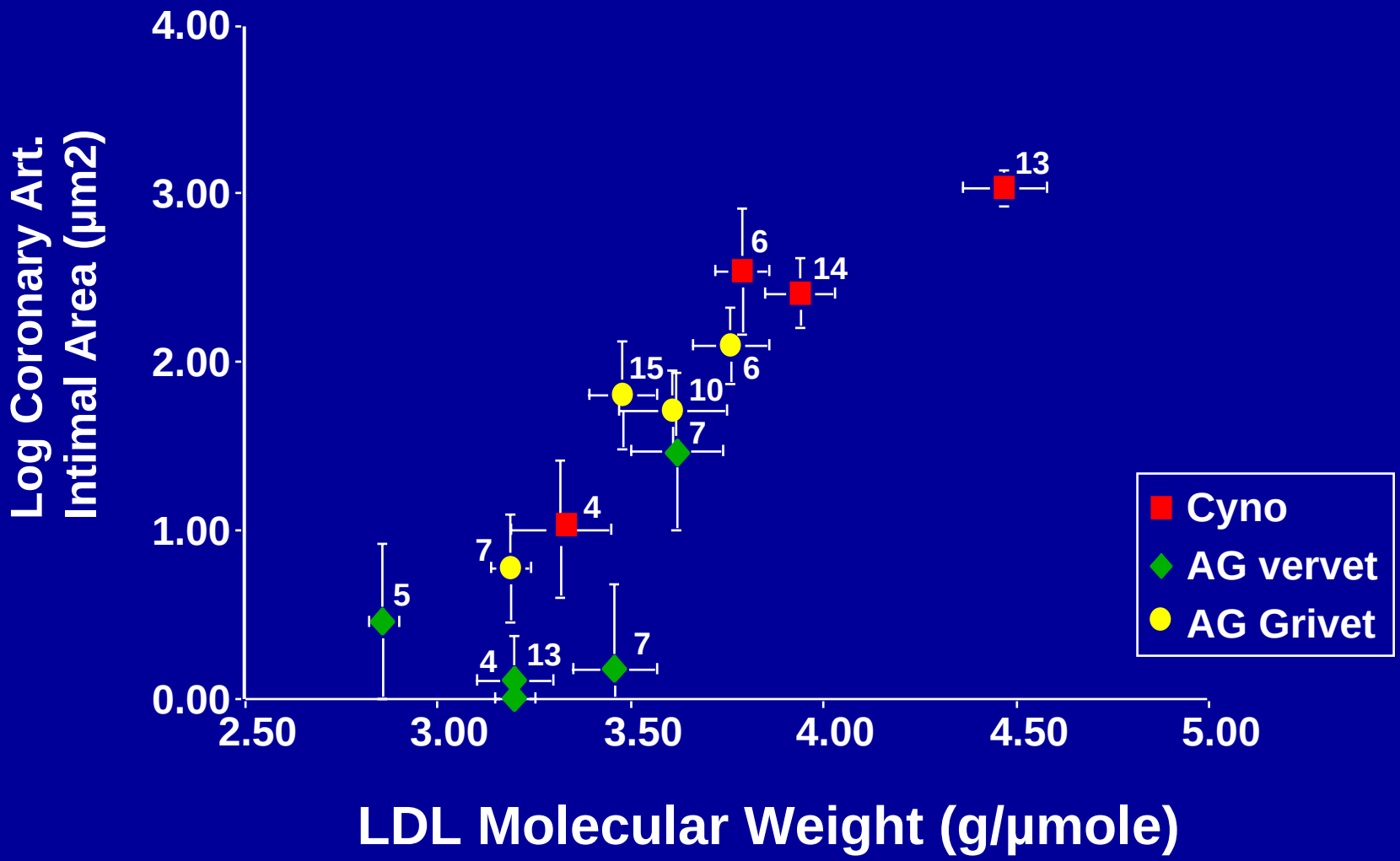


POLY MONO SAT

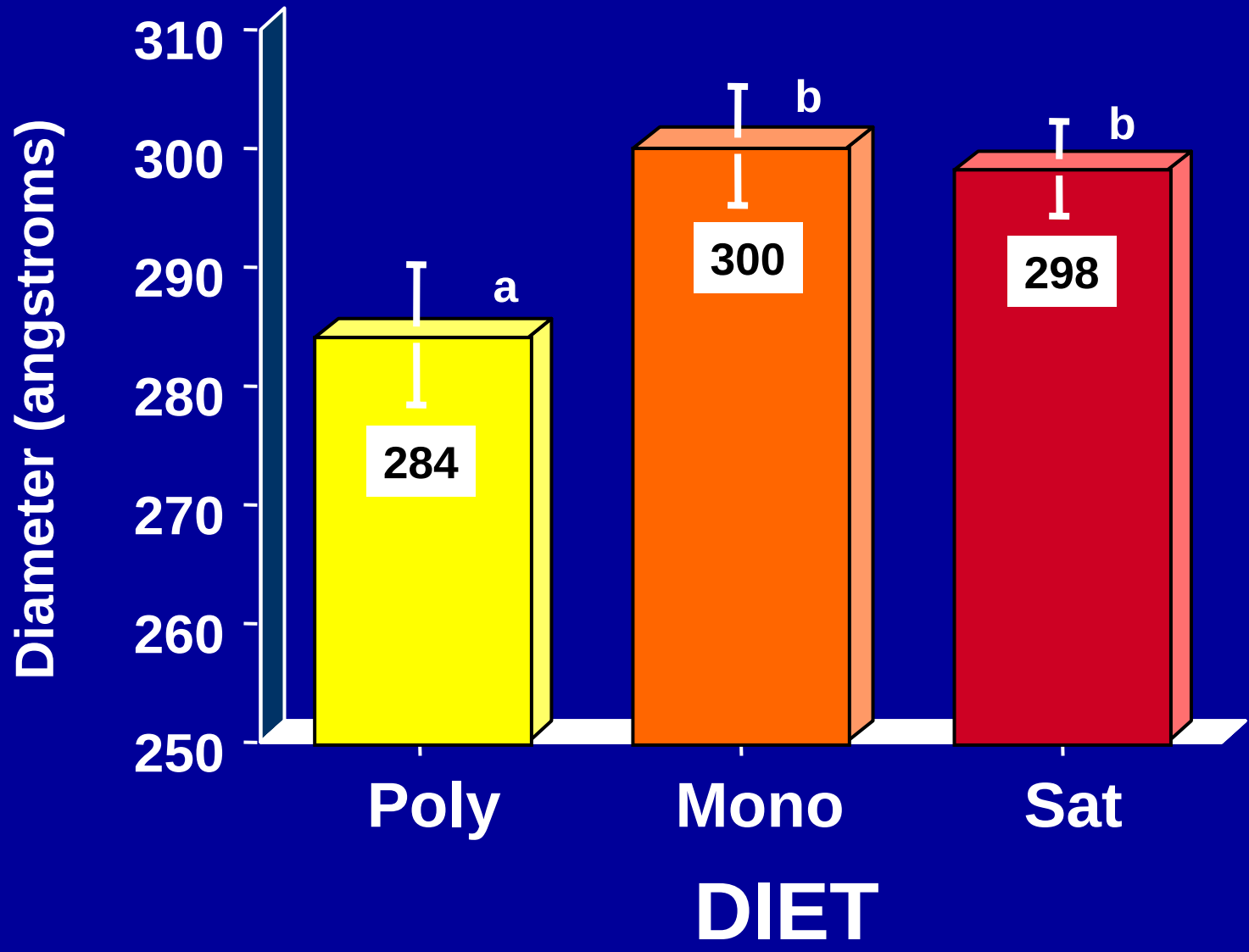
Primate Coronary Artery Athero is Related to Dietary Fat Type



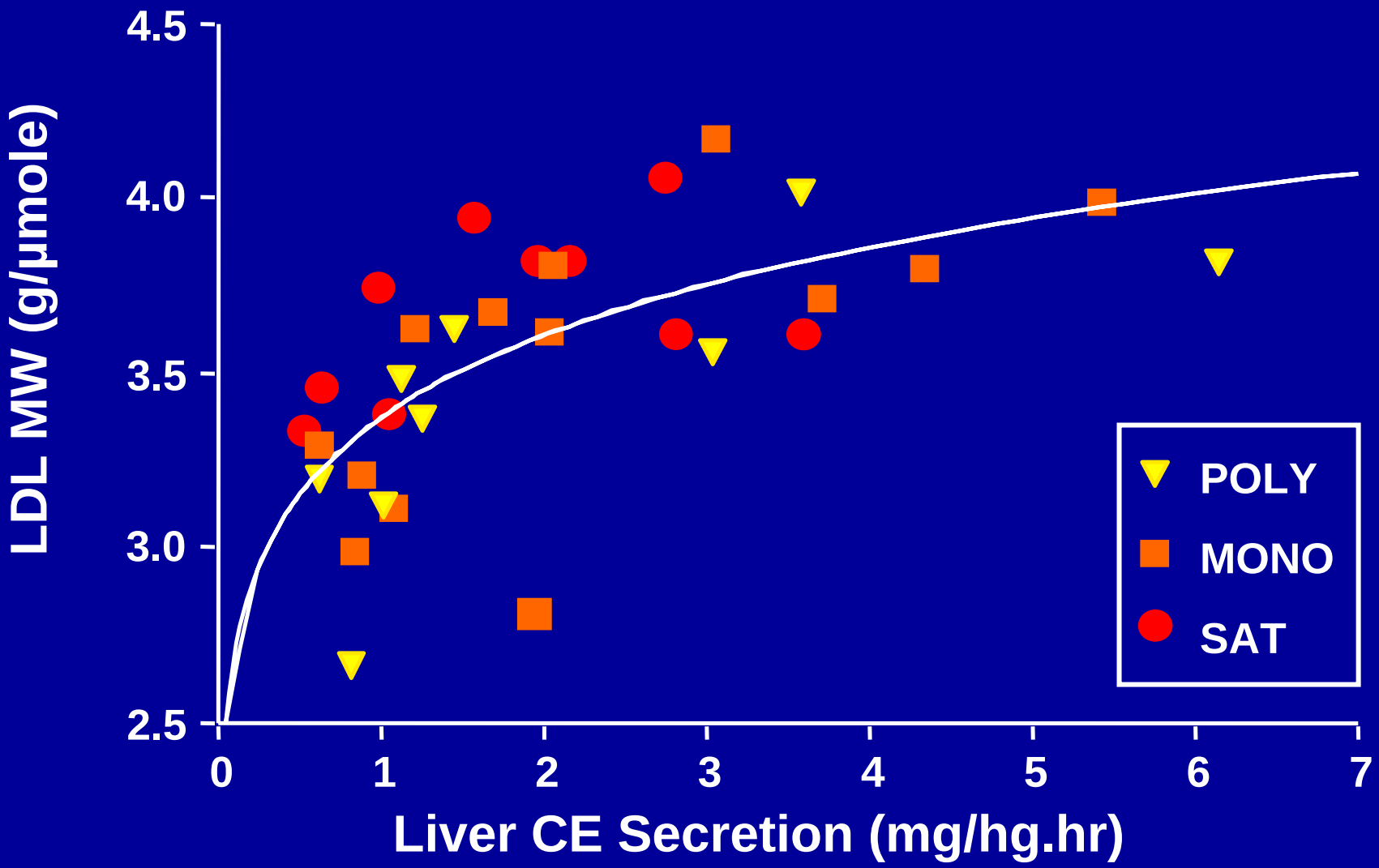
LDL Size Predicts Coronary Artery Atherosclerosis Extent in Monkeys



Plasma LDL Particle Size is Dependent on Dietary Fat Type

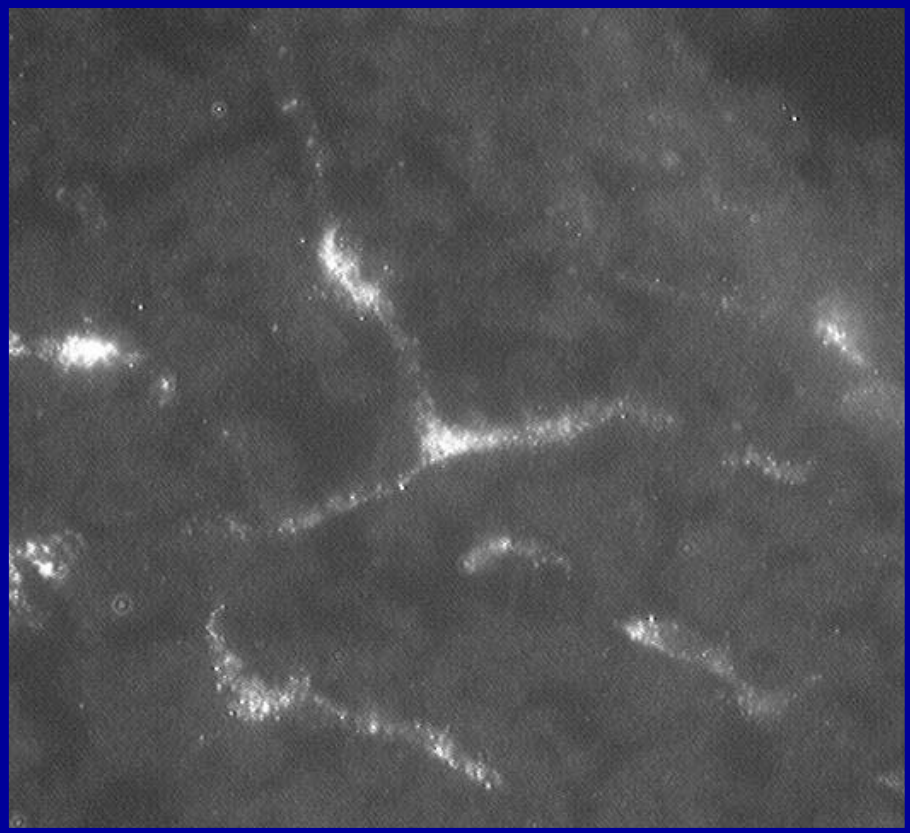


LDL Size is Highly Correlated to Liver CE Secretion Rate

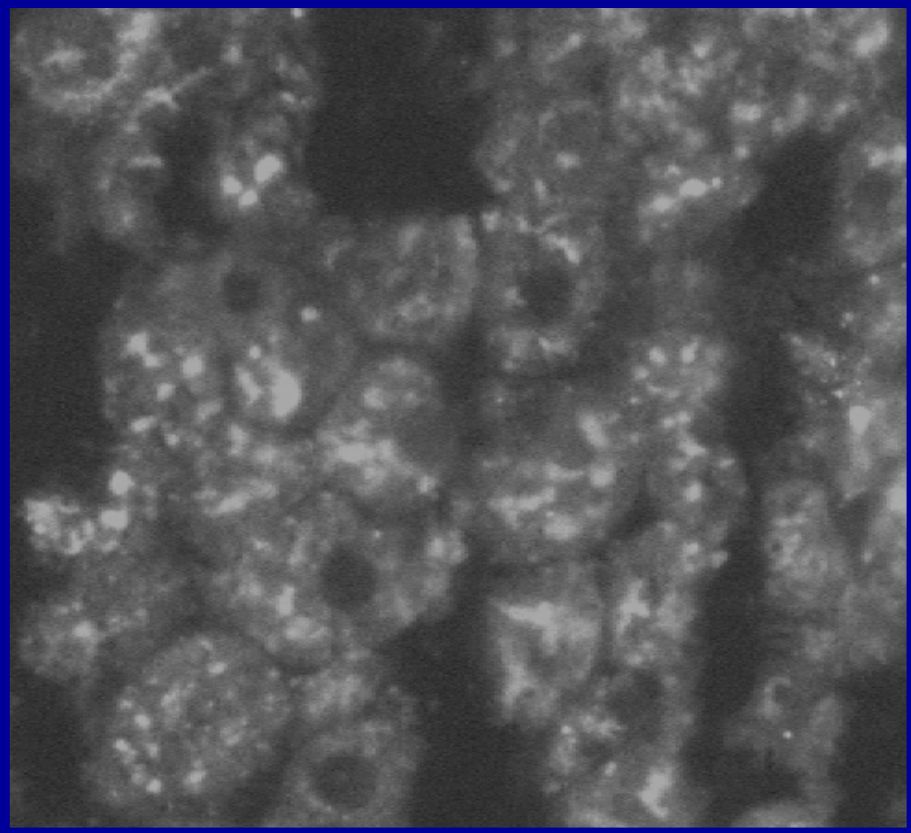


Localization of ACAT1 to Kupffer Cells and ACAT2 to Hepatocytes in Liver of African Green Monkeys

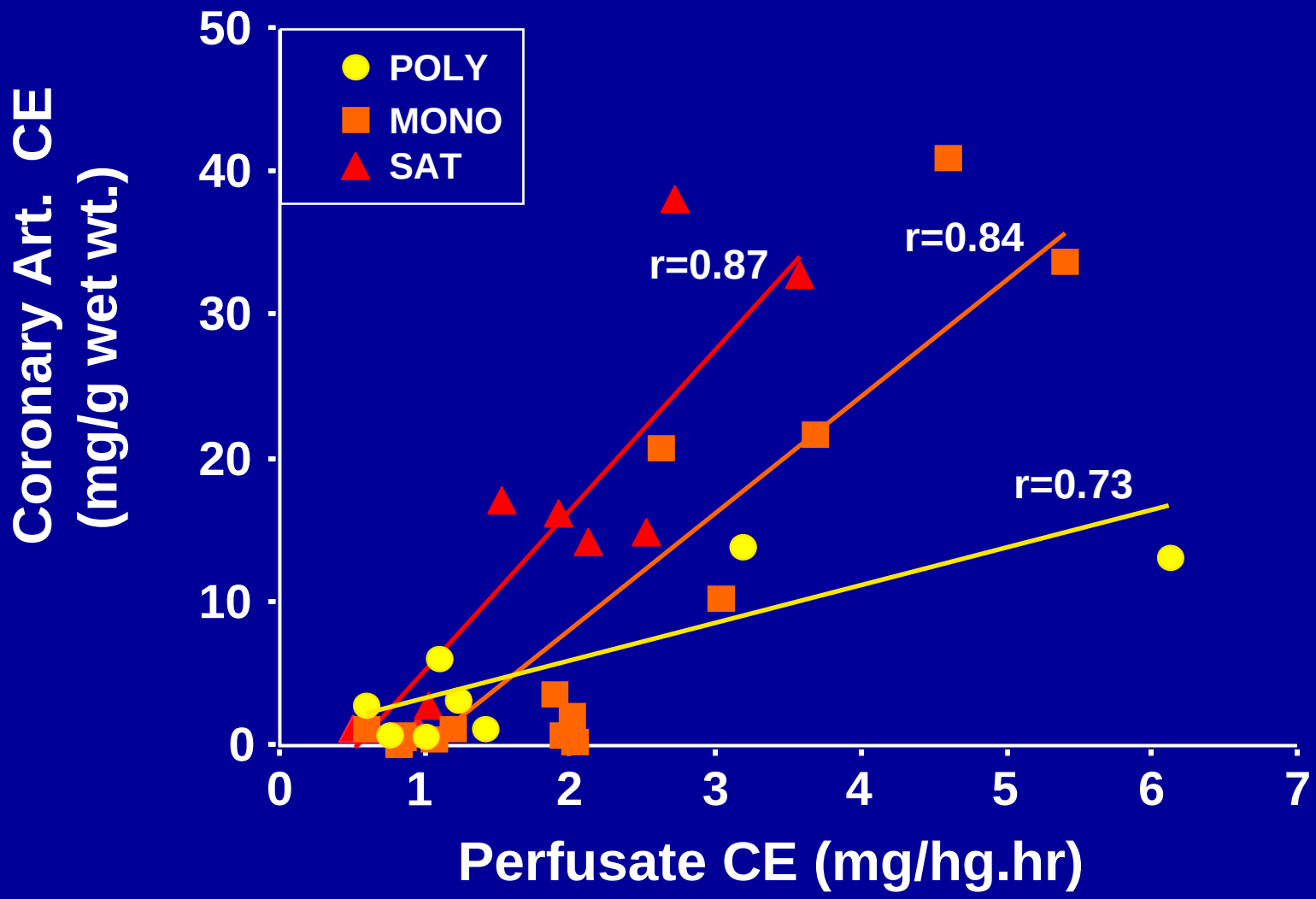
ACAT1



ACAT2

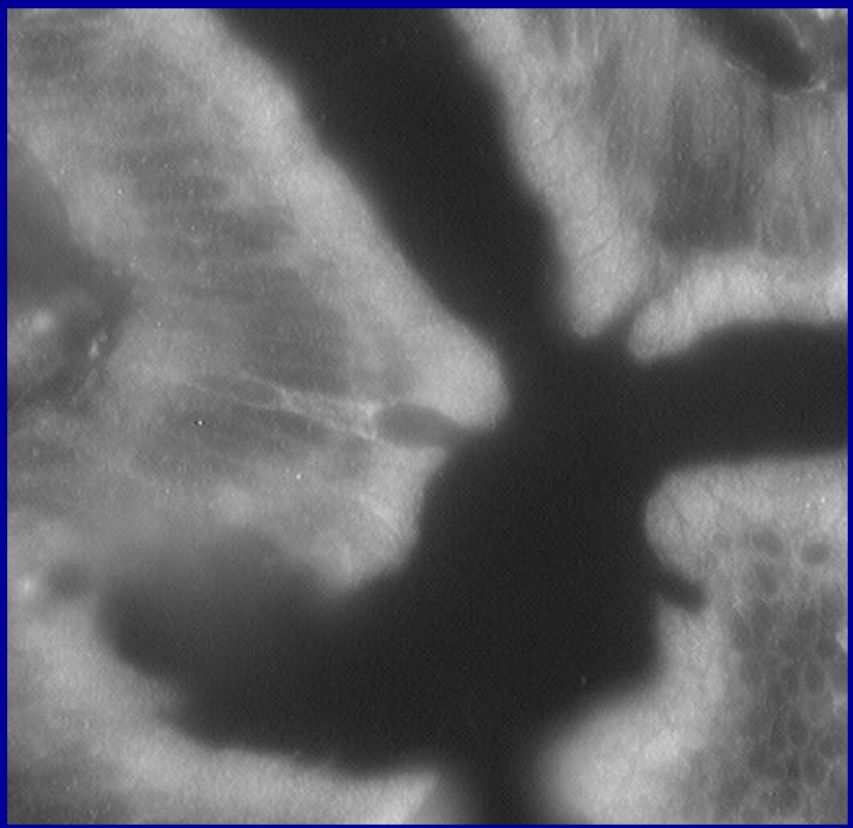


Liver Cholesterol Ester Secretion Rate is Strongly Related to Coronary Artery Atherosclerosis

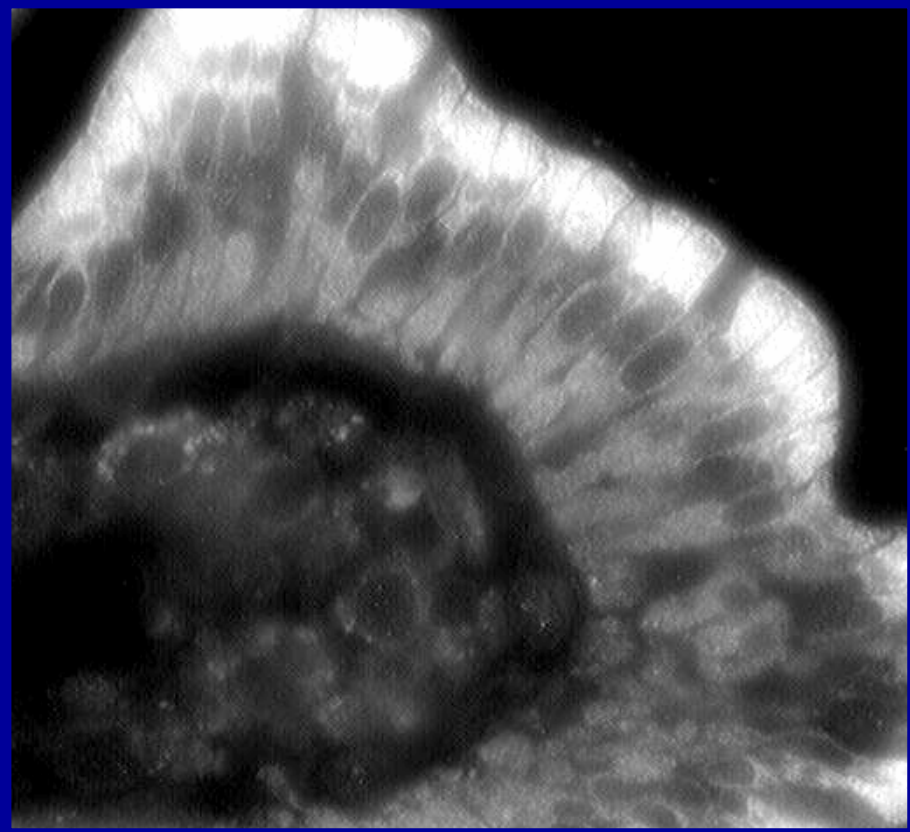


Localization of ACAT1 to Goblet Cells and ACAT2 to Enterocytes in Jejunum of African Green Monkeys

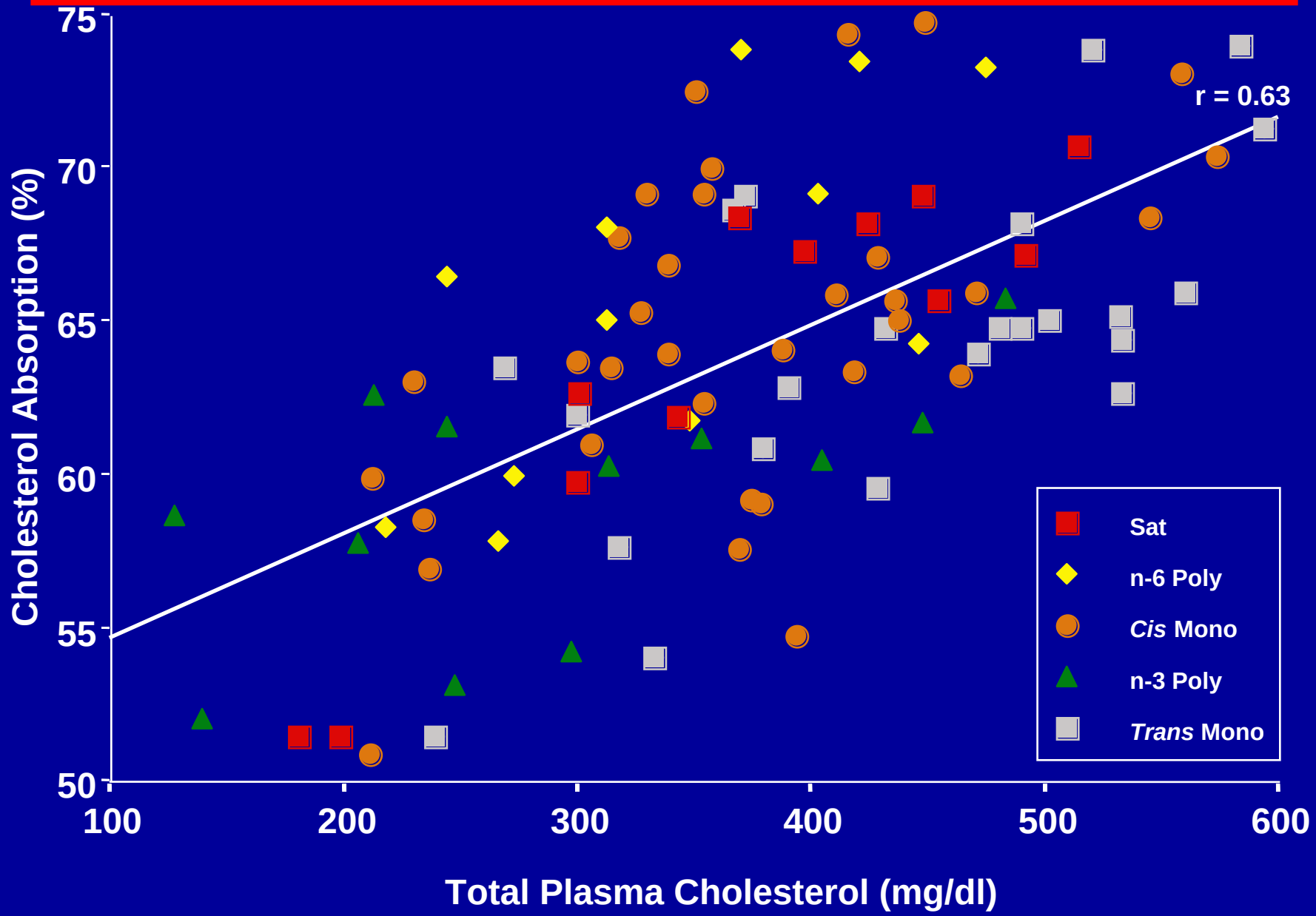
ACAT1



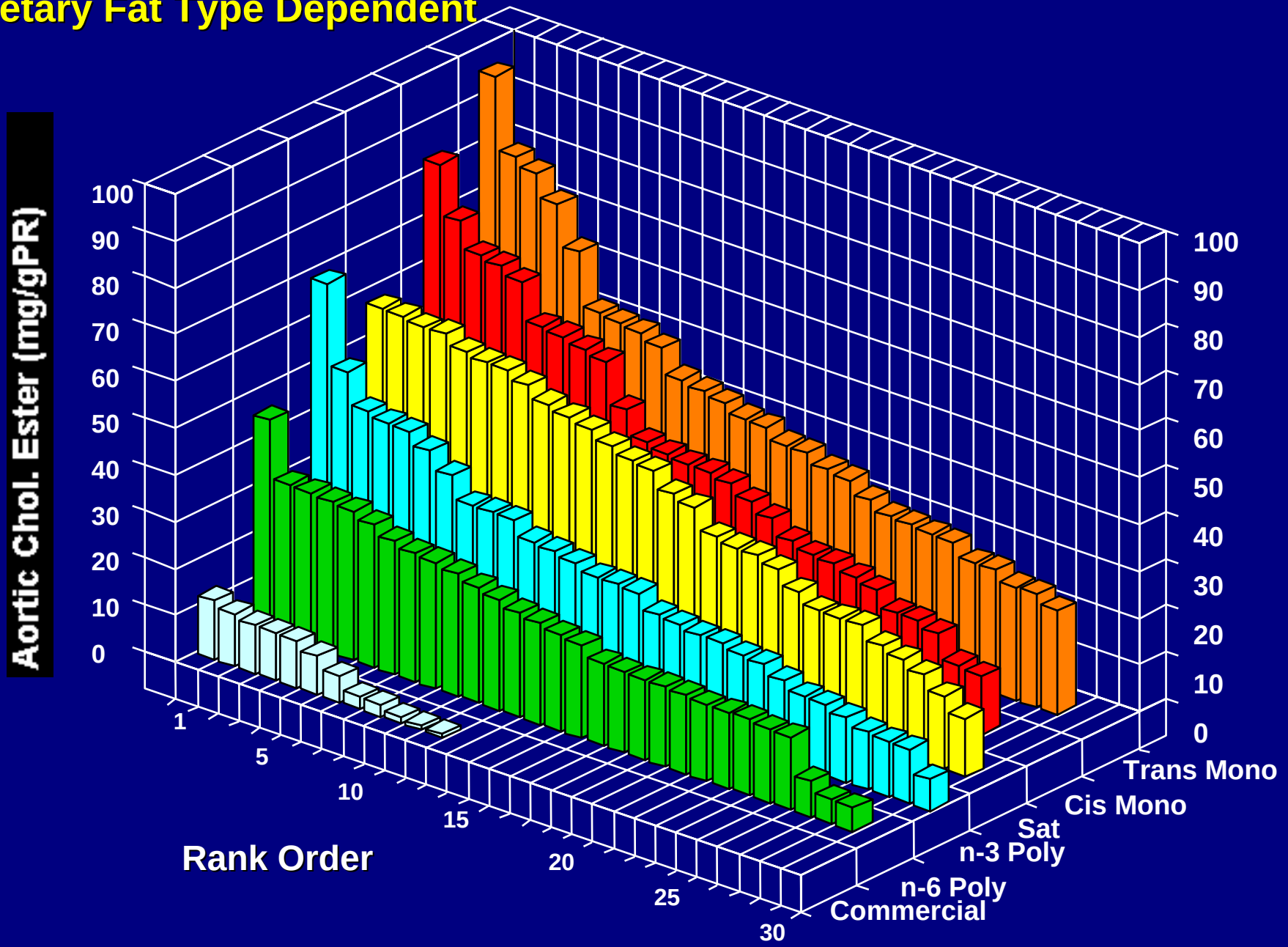
ACAT2



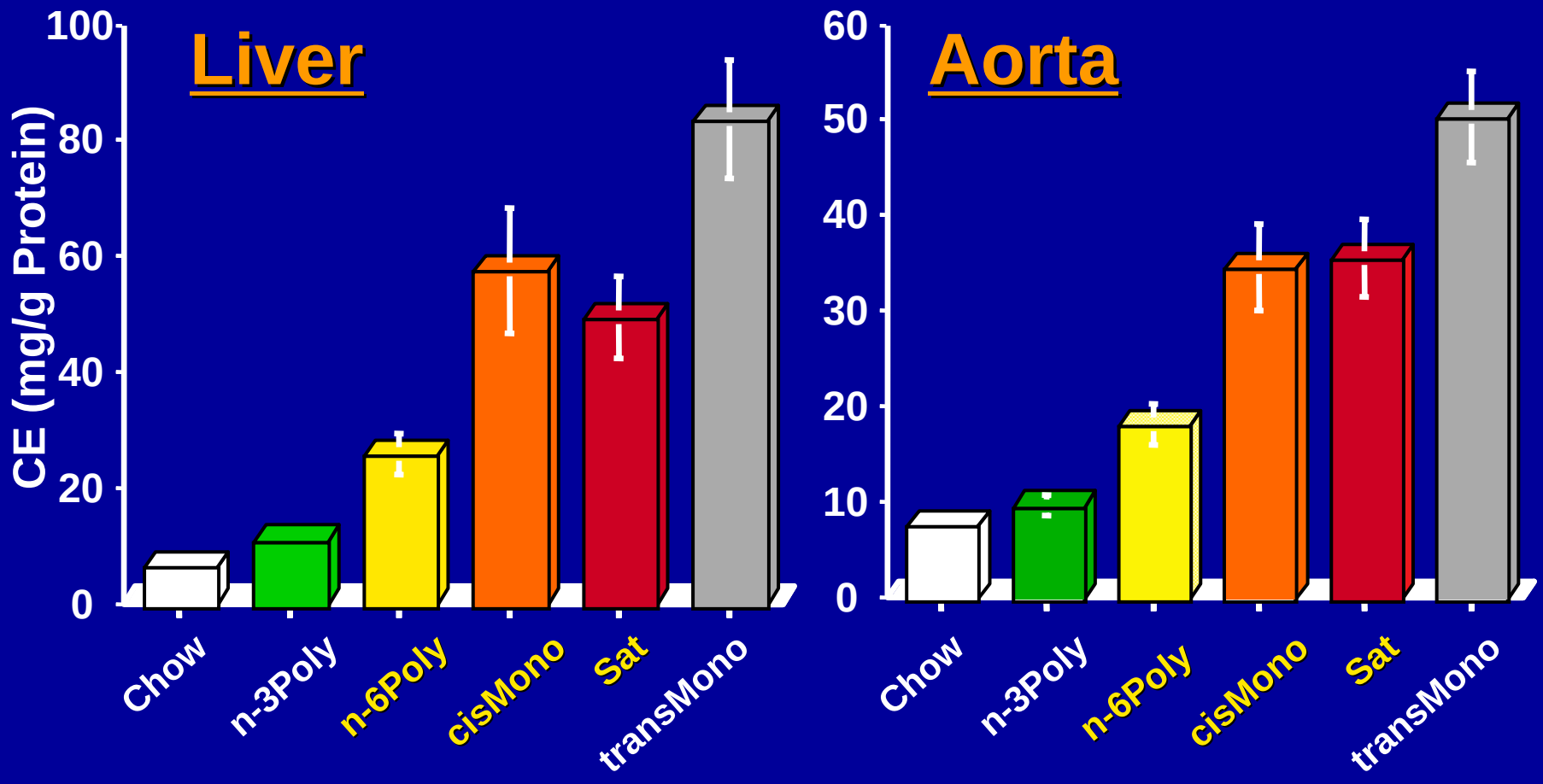
Percent Intestinal Cholesterol Absorption is Highly Related to Plasma Cholesterol but not Affected by Dietary Fat Type



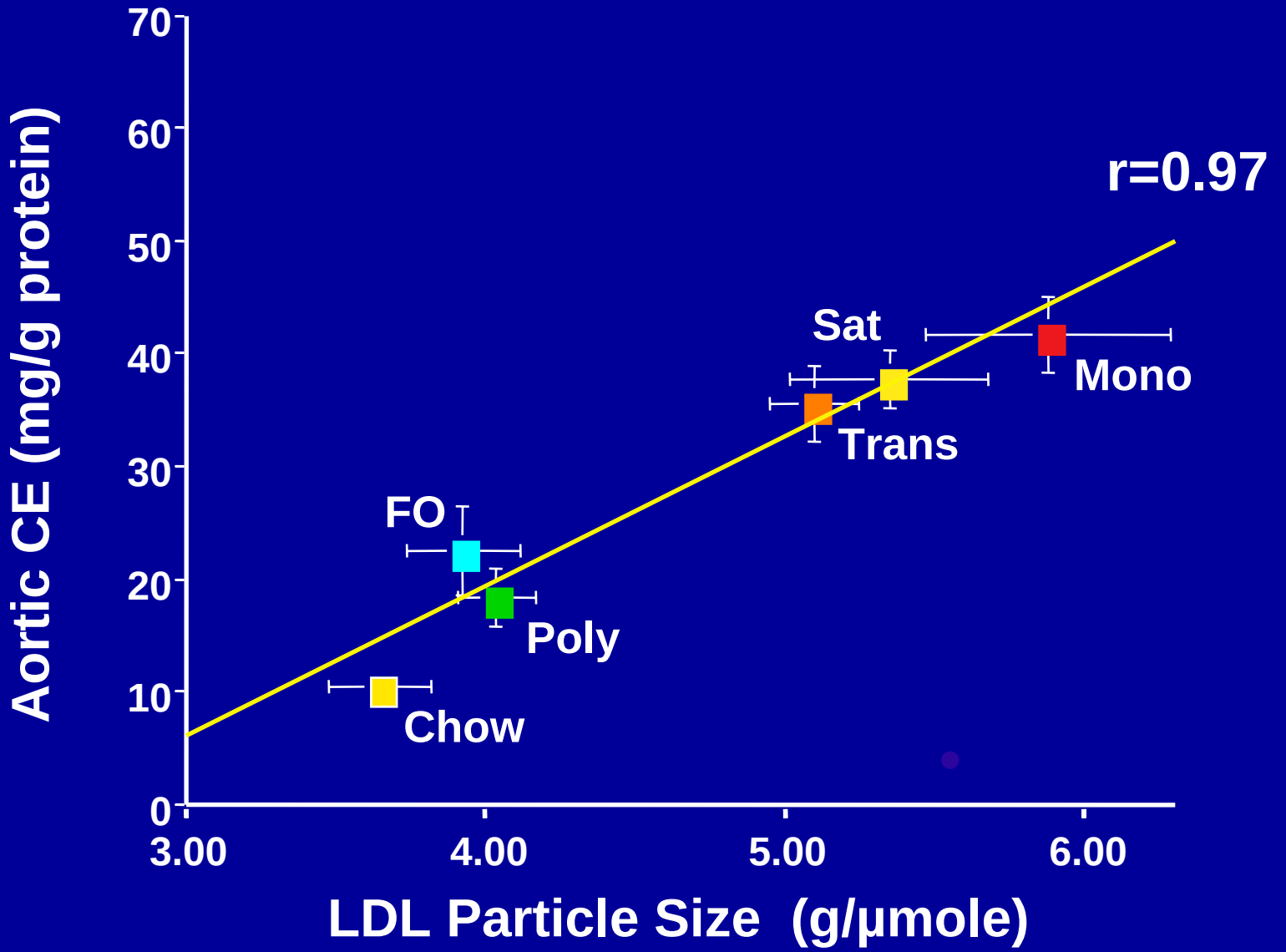
The Extent of Aortic Atherosclerosis in LDLr $^{-/-}$, ApoB100 Mice is Dietary Fat Type Dependent



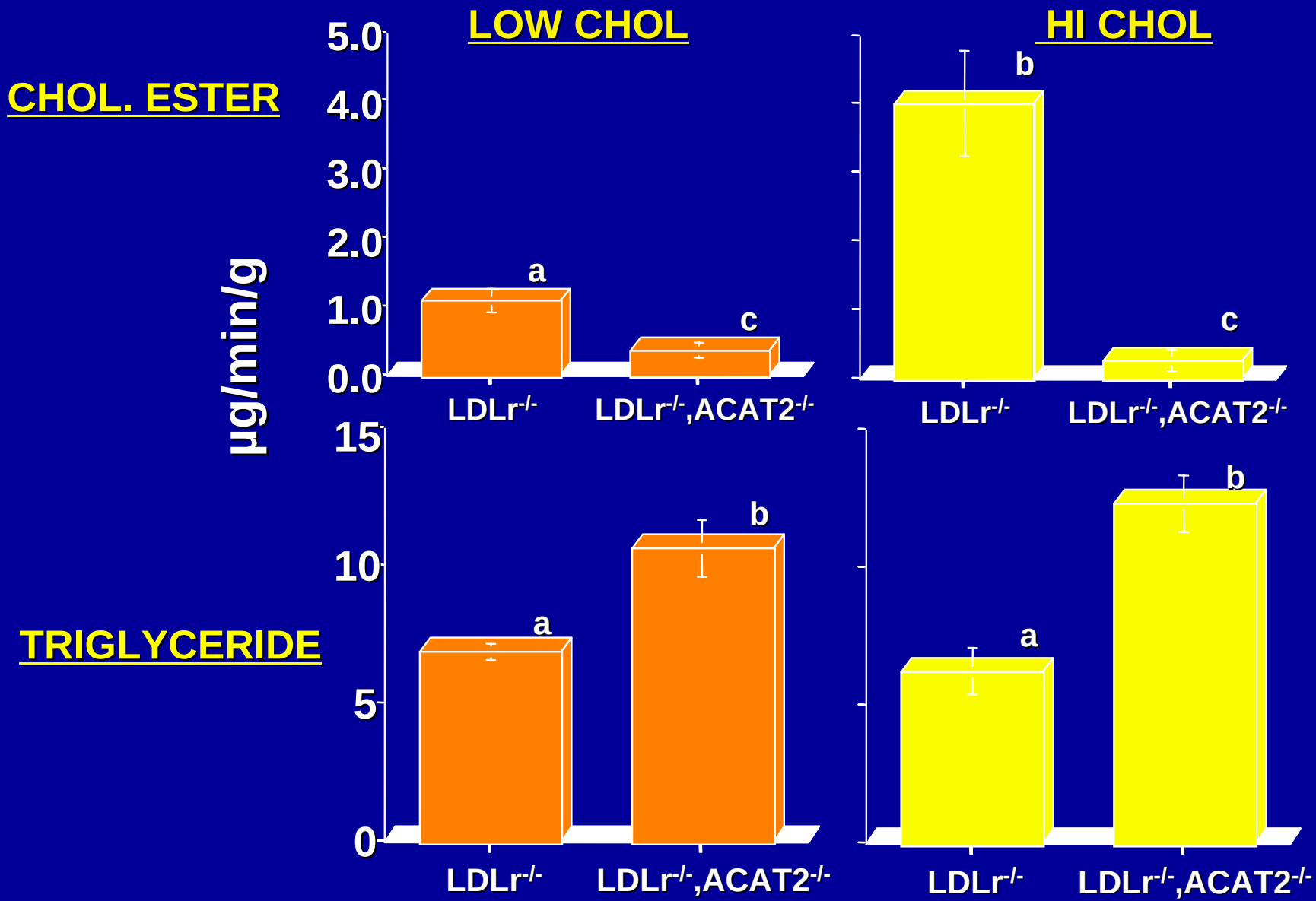
Dietary Fat Dependency of Cholesterol Ester Accumulation is Comparable in LDLr$^{-/-}$ Mouse Liver and Aorta



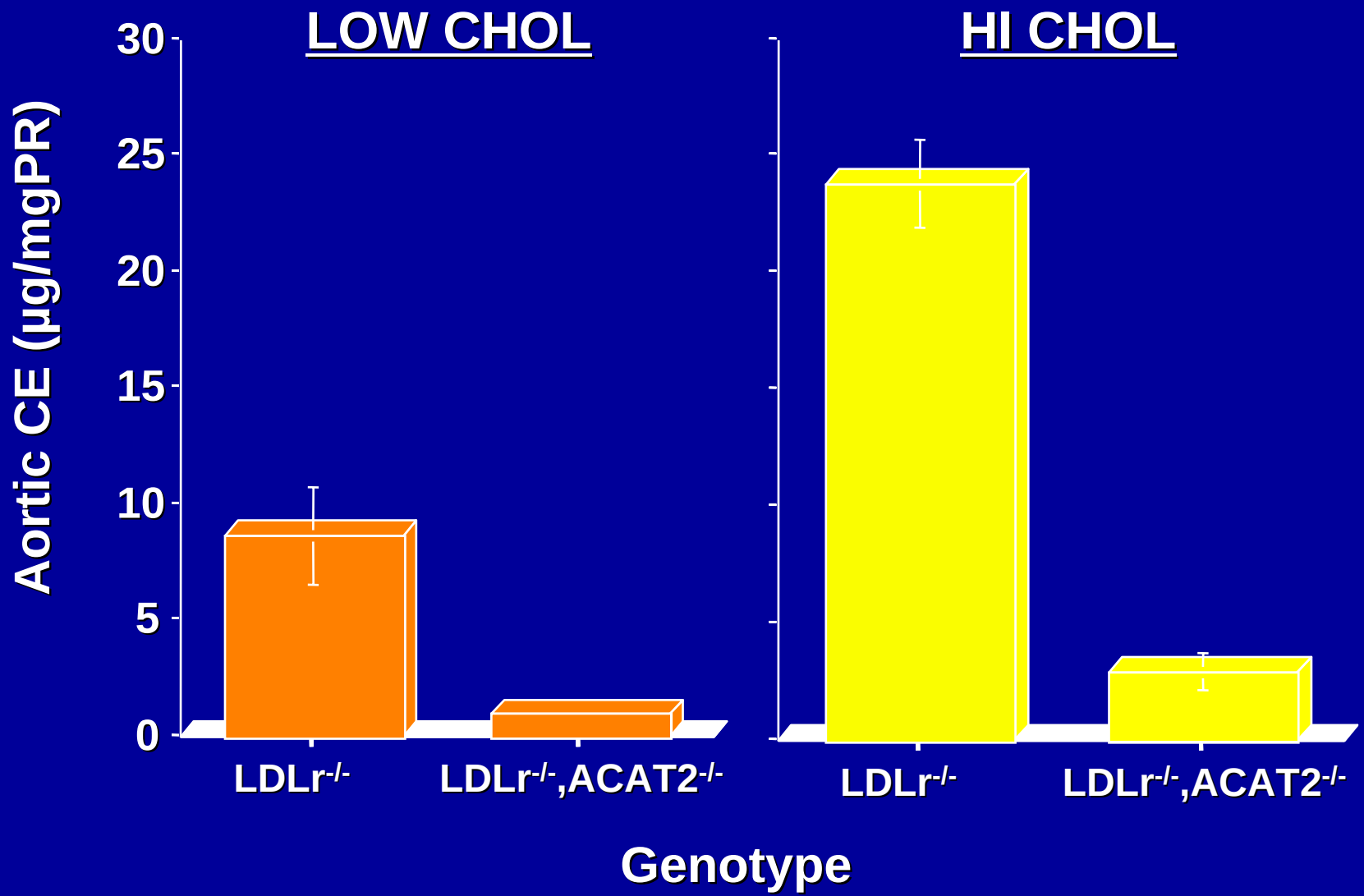
Aortic Atherosclerosis is Highly Related to LDL Particle Size as Modified by Dietary Fat Type in ApoB100-only LDLr$^{-/-}$ Mice



Perfused Liver Lipid Secretion Rates in LDLr$^{-/-}$ Mice With and Without ACAT2 Fed Low and High Cholesterol Diets



Aortic Atherosclerosis in LDLr$^{-/-}$ Mice With and Without ACAT2 Fed Low and High Cholesterol Diets



Conclusions

- **Dietary cholesterol and fat type are important factors in promoting the development of atherosclerosis**

- **Monkeys and mice show similar diet dependencies**

- **Indications are that effects on the liver enzyme ACAT2 may mediate many of the dietary fat and cholesterol effects to promote atherosclerosis**